REMARKS

Claim Rejections – 35 U.S.C. § 102

Claims 2-6 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Imai et al. (U.S. Patent No. 5,985,864; "Imai"). According to the Examiner, Imai discloses in Figure 3 an X-ray powder diffraction ("XRPD") pattern substantially similar to that shown in Figure 1 of the instant specification. The Examiner has provided a comparison of the XRPD patterns in Exhibit I. The Examiner also contends that the only difference between the process of claim 6 and Example 18 of Imai is the preheating to dissolve the starting material but that such step is not critical for crystallization and Imai apparently had donepazil base in solution. Applicants respectfully traverse this basis for rejection.

According to the MPEP § 2131:

> A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently descried, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 638, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Claims 2-5 are directed to crystalline donepezil HCl form VI having XRPD pattern substantially depicted as in Figure 1, while claim 6 is directed to a process for preparing crystalline donepezil HCl form VI having XRPD pattern substantially depicted as in Figure 1. Contrary to the Examiner's position, Imai does not disclose crystalline donepezil HCl Form VI, nor a process for its preparation, having each and every limitation as set forth in claims 2-6 of the instant application.

As noted in Applicants previous Amendment and Response submitted on February 14, 2007 (2/14/07 Amendment and Response"), the XRPD pattern for crystalline donepezil HCl form III, shown in Figure 3 of Imai, is substantially different than that for crystalline donepezil HCl form VI depicted in Figure 1 of the instant

application. The Examiner's Exhibit I only strengthens this conclusion. For example, the XRPD pattern for the instant crystalline donepezil HCl form VI has a substantial peak at about 11.5 degrees two-theta that is clearly absent from the pattern for the crystalline donepezil HCl form III of Imai, while the XRPD pattern for the crystalline donepezil HCl form III of Imai has a substantial peak at about 6.5 degrees two-theta that is clearly absent from the pattern for instant crystalline donepezil HCl form VI.

Applicants submit that by incorporation of the XRPD pattern of Figure 1, claims 2-6 adequately distinguish the instant crystalline donepezil HCl form VI from the donepezil HCl disclosed in Imai. As such, the Examiner has failed to make out a *prima facie* case for anticipation of the claimed polymorph. *See Ex parte Havens*, Appeal No. 2001-0091 for U.S. Pat. Appl. No. 08/732,254, now U.S. Pat. No. 6,452,007 (BPAI 2001) ("The examiner has provided no evidence or scientific reasoning to show that the delavirdine mesylate disclosed and claimed [in the prior art reference] is in the [claimed] crystal form. Therefore, the examiner has not made out a *prima facie* case of anticipation by inherency.").

Further evidence for the novelty of the claimed polymorph comes from the fact that the crystalline donepezil HCl form III of Imai has a melting point of 229-231° C (*see* '864 patent, col. 7, lines 12-13), whereas the melting point of the instant crystalline donepezil HCl form VI is 222-225° C (*see* page 8, lines 3-4). Since a chemical compound and its properties are inseparable, *see In re Papesch*, 315 F.2d 381, 391 (CCPA 1963), the difference in melting points must be an indication that the two compounds are distinct. *See Ex parte Polniaszek*, Appeal No. 2001-1805, U.S. Pat. Appl. No. 08/732,254, now U.S. Pat. No. 6,452,007 (BPAI 2003) ("[N]otwithstanding that the

claimed compound has the same formula as [the prior art compound], the examiner has not established that [the prior art compound] suggests appellants' specifically claimed polymorph. This is clearly demonstrated by the different melting points for the two compounds.").

Applicants also note that claim 6, which is directed to a process for preparing the novel crystalline donepezil HCl form VI, recites in step (b) reacting the donepezil/ethanol solution of step (a) with an HCl source at 25 to 35° C. In contrast, Example 18 of Imai, cited by the Examiner as an anticipatory process, performs an HCl reaction in an ice bath (*see* '864 patent, col. 15, lines 52-53), thereby providing another basis for the novelty of claim 6.

Accordingly, Applicants submit that claims 2-6 are not anticipated by Imai, and reconsideration of this basis for rejection is respectfully requested.

Claim Rejections – 35 U.S.C. § 103

Claims 2-6 and 8-12 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Imai in view of Doelker, *Ann. Pharm. Fr.* 60:161-176 (2002) ("Doelker"), Wikipedia, Article on Polymorphism, 1-2 (2006) ("Wikipedia"), Davidovich et al., *Am. Pharm. Rev.* 7:10, 12, 14, 16, 100 (2004) ("Davidovich"), or U.S Pharmacopia #23 (1995) ("USP #23"). According to the Examiner, Imai discloses the anticipatory product as claimed in claims 2-5 made by the process of claim 16. The differences between dependent claims 8-12 wherein variations of solvent systems was employed in the process of crystal preparation is said to be generically taught by Imai. Thus,

according to the Examiner one having ordinary skill in the art in possession of Imai is in possession of the instantly claimed variations.

According to MPEP § 706.02(j):

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The instant claims are directed to crystalline donepezil HCl form VI having X-ray powder diffraction pattern substantially depicted as in Figure 1. The references cited by the Examiner do not disclose, either alone or in combination, this particular polymorphic form.

As discussed above with respect to the § 102 rejection, the portions of Imai cited by the Examiner disclose the preparation of crystalline donepezil HCl form III, whose X-ray powder diffraction pattern shown in Figure 3 in Imai is substantially different than shown for the instant crystalline donepezil HCl form VI in Figure 1. In addition, form III has a melting point of 229-231° C, whereas the melting point of the instant form VI is 222-225° C. Form VI and Form III are clearly distinct polymorphic forms. There is no teaching or suggestion in Imai, however, that donepezil HCl exists as the form VI recited in the instant claims, nor is a method for its preparation disclosed. This alone is enough to overcome the Examiner's obviousness rejection. *See See Ex parte Havens*, Appeal No.

2001-0091 for U.S. Pat. Appl. No. 08/732,254, now U.S. Pat. No. 6,452,007 (BPAI 2003) ("The examiner's obviousness rejection seems to suffer the same infirmity as her anticipation rejection . . . . The examiner has provided no evidence or convincing reason why the prior art disclosure of delavirdine mesylate in an undefined state would have suggested the specific S and T crystal forms that are the subject of the instant claims.") (emphasis added).

As noted in Applicants previous Amendment and Response submitted on February 14, 2007, the proper test for obviousness in this case is not whether the possible existence of additional donepezil HCl polymorphs is suggested by the prior art, but whether it would have been obvious to make the particular donepezil HCl form VI disclosed and claimed in the instant application based on the prior art:

> The law of § 103 requires quite a different inquiry from that conducted by the ALJ. The correct inquiry is not whether the Bouzard monohydrate [polymorph] could have been produced by manipulation of other cefadroxil processes, once the existence of the Bouzard monohydrate was known. The question is whether it would have been obvious to make the Bouzard monohydrate, based on the prior art.

Bristol-Myers Co. v. U.S. Int'l Trade Comm'n, 892 F.2d 1050, 1989 WL 147230 (Fed. Cir. Dec. 8, 1989) (unpublished decision) (emphasis added).

Here, the references cited by the Examiner suggest at most the possibility of additional donepezil HCl polymorphs. The Examiner has pointed to nothing in the cited references, either alone or in combination, which would suggest to one skilled in the art the particular donepezil HCl form VI disclosed and claimed in the instant application, or a method for its preparation. *See Ex parte Polniaszek*, Appeal No. 2001-1805, U.S. Pat. Appl. No. 08/732,254, now U.S. Pat. No. 6,452,007 (BPAI 2003) ("The prior art relied

upon by the examiner does not teach this specific polymorph as claimed by the appellants. The Examiner failed to demonstrate that the prior art even recognized that the claimed compound exists in different polymorphic forms, or that there is a known or obvious way to manufacture the specific polymorphic form claimed.").

Accordingly, Applicants submit that claims 2-6 are not *prima facie* obvious over Imai in view of Doelker, Wikipedia, Davidovich or USP #23, and reconsideration of this basis for rejection is respectfully requested.

Claim Objections

Claims 8-12 are objected to under 37 CFR § 1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. According to the Examiner, the dependent claims are drawn to scope of "comprising" alcohol or ether, which is broadening of the base claim wherein only alcohol or ether was the solvent. Applicants respectfully traverse this basis for objection.

Claims 8-12 are directed to a process for preparing the crystalline donepezil HCl form VI of claim 2. Contrary to the Examiner's position, claim 2 does not recite alcohol or ether, or any solvent for that matter. Because claims 8-12 specify how the crystalline donepezil HCl form VI of claim 2 is prepared, they do limit the subject matter of the base claim, and thus are proper dependent claims. *See* MPEP § 608.01(n), part III.

Accordingly, Applicants submit that claims 8-12 meet the requirements of 37 CFR § 1.75(c), and reconsideration of this basis for objection is respectfully requested.

CONCLUSION

Applicants submit that that claims 2-6 and 8-12 are now in condition for allowance, early notice of which would be appreciated. If any outstanding issues remain, the Examiner is invited to telephone the undersigned at the number indicated below to discuss the same. No fees are believed due at this time. If, however, any fees are due, the Commissioner is authorized to charge any such fee to our Deposit Account No. 50-3221.

Respectfully submitted,

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